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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,230	09/13/1999	KEVIN L. GUNDERSON	393382001600	3919

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EXAMINER

FORMAN, BETTY J

ART UNIT PAPER NUMBER

1634

DATE MAILED: 09/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/394,230	Applicant(s) GUNDERSON ET AL.	
	Examiner BJ Forman	Art Unit 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 August 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☒ they raise the issue of new matter (see Note below);
 - (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: see attached Continuation of Advisory Action.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-18.

Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☒ Other: Interview Summary

Continuation of Advisory Action

The amendments will not be entered because they add limitations not previously considered or searched. Therefore, the amendments would require further search and consideration.

Additionally, the amendments will not be entered because they potentially add new matter. Applicant points to page 19, lines 4-8 and page 29, lines 23-27 for support for the newly added limitation. The cited passages are provided below.

page 19, lines 4-8:

These photolithographic and fabrication techniques enable each probe sequence to occupy a very small area on the support. For example, a probe array of 0.25 mm could have 4×10^5 or 10^6 features. Further details on achieving the desired probe from a 1000 to 10 or density can be found in U.S. Patent No. 5,510,270, the disclosure of which is incorporated by reference.

page 29, lines 23-27:

Complete n-mer deoxypolynucleotides were synthesized on derivatized glass substrates using light-directed photochemistry as previously described by Pease et al., (1994) Proc Natl Acad Sci USA 91, 5022-6, herein incorporated in its entirety by reference. 8-mer arrays are synthesized with 50x50 pm probe feature sizes and n-mers with 25x25 μm probe feature sizes.

The cited passages do not provide support for the newly claimed "discrete probe features, each probe feature comprising multiple probes, all having the same sequence within a discrete known location within the array". Because the cited passages do not provide support for the proposed amendments, the amendments potentially introduce new matter and therefore raise issues of new matter.

Response to Arguments

Applicant argues that one of ordinary skill would not reasonably expect from the confusing and speculative teaching of Cantor et al to produce an array with a complete set of n-mer that could successfully work in the methods of the present invention. Applicant cites passages of Cantor et al which differ from the instant invention to support the conclusion that the array of Cantor et al would not work successfully. Applicant further argues that the combination of Southern and Lipshutz with that of Cantor does not provide a reasonable expectation of success.

The arguments have been considered but are not found persuasive for numerous reasons. First, Cantor et al specifically teach a complete n-mer (Column 6, lines 3-5) and they teach clearly teach probe arrays (Column 7, lines 12-24 and Claim 1-18). Second, the courts have stated that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.(see MPEP § 716.01(c))

Finally, the courts have further stated that when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980) (See MPEP § 2121 and § 716.07).

For the reasons stated above, Applicant's arguments regarding no reasonable expectation of success are not found persuasive.

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Applicant argues that Southern et al do not teach every element of the instant invention and Applicant argues that Lipshutz et al do not teach every element of the instant invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the examiner has used hindsight reconstruction to arrive at the instant invention. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant further argues that there is no motivation to combine the teachings of Cantor with those of Southern and Lipshutz. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine was clearly provided in the final office action as summarized below.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the complete n-mer hybridization detection and analysis of Cantor et al. with the complete n-mer hybridization comparison analysis of Southern whereby comparing hybridization patterns reveals differences between the target and reference and

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eliminates the need for sequencing the target sequence (Column 3, lines 52-62) and wherein the hybridizations are extremely sensitive because complete n-mer hybridizations are performed under highly stringent conditions to discriminate between single mismatch sequences as taught by Southern (Column 10, line 57-67-Column 11, line 4) for the expected benefits of identifying mutations accurately, efficiently and economically i.e. identifying mutations under highly stringent conditions without the time and labor consuming sequencing reactions.

Cantor et al and Southern do not teach the arrays comprise perfect match and mismatch probes wherein mutation determination is via normalizing hybridization intensities utilizing the mismatch and perfect match probes. Lipshutz et al also teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5, lines 21-24) on an array comprising perfect match and mismatch probes (Example 2, Column 12, lines 15-32) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 9, line 36-Column 10, line 56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Lipshutz et al to the mutation detection of Cantor et al and Southern to thereby easily and accurately identify mutations as taught by Lipshutz et al (Column 9, line 36-Column 10, line 56).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this

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application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to be 'BJ Forman', with a stylized, sweeping flourish extending upwards and to the right.

BJ Forman, Ph.D.
Primary Examiner
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September 10, 2003